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(54) REACTION PRODUCTS OF [illegible]

PATENTS ACT 1949

SPECIFICATION NO 1334933

SLIP NO 2

The following corrections were allowed under Section 76 on 14 August 1974

Page 6, line 126, *for* cermatosic *read* dermatosic

THE PATENT OFFICE
3 September 1974

R 77172/6

[illegible] reaction product of calcium ascor- [illegible] as the ureide of calcium ascorbate wherever the same is used medically pharma- instance nent of cies, or agent or ms in the as, bruises, lips, itching, nditions in- mia, that is ts of using m its pro- antiphlo- ng, anti- iating, all ible local applica- of high parations e treat- where ffects of

ERRATA

SPECIFICATION No. 1,334,933

Page 4, line 58, *for* noncatilytic *read* noncatalytic

Page 9, line 35, *for* monohydrous *read* nonhydrous

THE PATENT OFFICE
19th July, 1974

[illegible] by providing extremely stable, clear, homogeneous consistencies, having the therapeutic properties of calcium ascorbate and, in addition, also the antimicrobial properties of the nonhydrous 1,2-dihydroxypropane constituent therein where the same is used as the coconstituent with the calcium ascorbate in the reaction products.

The preparation and availability of such high concentration calcium ascorbate prepara- [illegible] calcium ascorbate may be of value, for instance as a new use in form of a suckable concentrate therapeutic agent which slowly dissolves in the mouth and exerts a direct effect on infectious conditions and inflammations without being cariogenic, for instance in form of a solid hard candy-like product supplying up to 672 mgs of active l-ascorbic acid per gram of product and up to 78 mgs ionic calcium and exerting a strong local antimicrobial and antivirus effect not only by

SEE ERRATA SLIP ATTACHED

SEE CORRECTION SLIP ATTACHED

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(19)

(54) REACTION PRODUCTS OF CALCIUM ASCORBATE AND PREPARATION CONTAINING THEM

(71) I, GERHARD WILLIAM AHRENS, a citizen of the United States of America of 1781 East 15th Street, Brooklyn, State of New York, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new therapeutic calcium ascorbate preparations and novel products containing such preparations.

The invention provides a method of preparing the reaction product of calcium ascorbate dihydrate with a nonhydrous di- or trihydroxypropane compound which comprises reacting the admixed calcium ascorbate dihydrate and nonhydrous hydroxypropane compound in a closed vessel, under agitation, at a reaction temperature of from 225 to 255°F in the presence of a protective, non-destructive environment for the necessary period of time for formation of a clear, homogeneous and stable reaction product of calcium ascorbate.

The method according to the invention enables one to obtain preparations having a high concentration of calcium ascorbate. The reaction products of calcium ascorbate with the nonhydrous hydroxypropane compound may have a larger concentration of calcium ascorbate dihydrate present therein than a nonhydrous hydroxpropane compound would normally have dissolved therein.

The calcium ascorbate preparations of the invention, are characterized by possessing extremely stable, clear, homogeneous consistencies, having the therapeutic properties of calcium ascorbate and, in addition, also the antimicrobial properties of the nonhydrous 1,2-dihydroxypropane constituent therein where the same is used as the co-constituent with the calcium ascorbate in the reaction products.

The preparation and availability of such high concentration calcium ascorbate preparations in a stable form opens up an entire new field of applications for calcium ascorbate. The possibility of using calcium ascorbate preparations forthwith at higher and more stable concentrations than ever before this invention constituents a major advance in medical and therapeutic techniques of employing and utilizing the wondrous properties of calcium ascorbate. It is obvious that higher concentrations of applied calcium ascorbate would increase its therapeutic effectiveness accordingly and this, combined with the higher stability, should account for a major increase in the utility of calcium ascorbate wherever the same is used medically, pharmacologically and dermatologically, for instance as parenteral preparations in the treatment of Vitamin C and/or calcium deficiencies, or as a novel liniment-type therapeutic agent or as ingredient of anhydrous skin creams in the treatment of sores, wounds, burns, bruises, cuts and cracks of the skin and lips, itching, infective and dermatosic skin conditions including such caused by hypocalcemia, that is in all conditions where the benefits of using calcium ascorbate are derived from its properties such as being hemostatic, antiphlogistic, antitraumatic, antisensitizing, antidermotosic, soothing and itch alleviating, all of which depending on the available local concentration of the same. Other new applications because of the new availability of high concentration calcium ascorbate preparations of high stability include its use in the treatment of conditions of the oral cavity where the antipyorrheaic and anticariogenic effects of calcium ascorbate may be of value, for instance as a new use in form of a suckable concentrate therapeutic agent which slowly dissolves in the mouth and exerts a direct effect on infectious conditions and inflammations without being cariogenic, for instance in form of a solid hard candy-like product supplying up to 672 mgs of active l-ascorbic acid per gram of product and up to 78 mgs ionic calcium and exerting a strong local antimicrobial and antivirus effect not only by

virtue of the known such effects of high local concentrations of l-ascorbic acid but also by virture of the presence in the product of 1,2-dihydroxypropane which is the preferred hydroxypropane derivative with which the calcium ascorbate dihydrate constituent of the preparation of the invention has been reacted in the manufacture of such high concentrated solid and hard candy-like calcium ascorbate products. Closely aligned with the above usage of said hard candy-like high concentrated calcium ascorbate product is its new use as ingredient of candies and/or lozenges to counteract the cariogenic effects of sugar and other essential constituents in such candies and lozenges, thereby however, not only conferring anticariogenic properties upon said candies and lozenges but also, in addition, the general therapeutic effects of calcium ascorbate and the antimicrobial effects of 1,2 dihydroxypropane, which constituent is also in this case the preferred hydroxypropane derivative with which the calcium ascorbate constituent of the preparation of the invention has been reacted in the course of manufacturing the same. Although the employment of trihydroxypropane in preparing these hard candy-like reaction products is feasible, it is not the preferred form for practical reasons, as it is not as brittle and easy workable product for incorporation into a candy mass as the product derived from the employment of 1,2-dihydroxypropane, which can be easily powdered and feels dry to the touch in contrast to the more tenacious, less brittle and more difficult to pulverize product yielded by employing trihydroxypropane.

A further new use made possible by the invention is the employment of the high concentration calcium ascorbate contents preparation as an anti-cariogenic additive to drinks such as sodas, lemonades and fruit juices to counteract the cariogenic effects of ingredients in said drinks and at the same time adding active l-ascorbic acid or Vitamin C, in the non-cariogenic form as calcium ascorbate, to the said drinks as well as ionic calcium. The preferred hydroxypropane derivative for use in preparations of the invention to serve as additive to drinks is the trihydroxypropane for the implicit reason of having a sweetish taste in contrast to the acridic taste of 1,2-dihydroxypropane which, although allowed by the U.S. Food and Drug Administration for applications in foods, would be not as desirable therein as is trihydroxypropane, this being the reason why the application of the latter must also be preferred when it comes to consider preparation of calcium ascorbate reaction products intended for parenteral applications.

As ingredient of nonhydrous stable skin creams, the use of the preparations of the invention constitutes the creation of the first smooth, stable and homogeneous skin cream with calcium ascorbate ever produced and represents the first such skin cream capable of actively supplying active l-ascorbic acid or Vitamin C and ionic calcium to the skin by ionizing of calcium ascorbate which the latter undergoes when coming in contact with living tissue and skin. The amounts of available l-ascorbic and ionic calcium from the ionization of the said calcium ascorbate contained in such creams depends of course on the amount of calcium ascorbate available as a constituent of such creams but amounts to from 34 mgs to 350 mgs of active l-ascorbic acid and from 4 mgs to 40 mgs ionic calcium for each gram of cream containing amounts of calcium ascorbate constituents as specified in the example of two such creams cited in this specification.

Although the employment of hydrous hydroxypropane compounds having 2 or 3 hydroxy groups e.g. the 1,2-dihydroxypropane or the trihydroxypropane in making solutions of calcium ascorbate dihydrate therewith would give higher concentrated calcium ascorbate preparations, such cannot be employed if a stable end product is to be obtained. Such preparations lack stability and are subject to formation of breakdown products therein and degradation as result of storage. There is, however, the possibility of preparing products comprising calcium ascorbate dihydrate dissolved in nonhydrous hydroxypropane compounds of the kind employed also in the preparations of the invention. Such products have been made but contain only minute concentrations of calcium ascorbate dihydrate as the latter can be dissolved in such nonhydrous hydroxypropane compounds only in extremely low concentrations, for instance by agitating mixtures of these ingredients for extended periods of time too uneconomical to be useful or by heating such mixtures to the limiting temperature exposure levels of between 130°Fa to 140°Fa at which no damage to the calcium ascorbate dihydrate constituent in such mixture would occur if limited to relatively short periods of time and continuing such heating for several days in a row in the attempt to increase the rate of dissolution of the calcium ascorbate dihydrate in the nonhydrous hydroxypropane compound having 2 or 3 hydroxy groups e.g. the 1,2-dihydroxypropane or trihydroxypropane. Even though quite homogeneous and clear solutions could thus be obtained, only a slight but still unsatisfactory increase in the concentration of dissolved calcium ascorbate dihydrate in the said nonhydrous hydroxypropane compounds was brought about. No reaction, however, between the calcium ascorbate dihydrate and the nonhydrous hydroxypropane compounds has taken place and no reaction product therefore was obtained having far higher calcium ascorbate dihydrate concentrations than would normally dissolve in

nonhydrous hydroxypropane compounds. All that could be and was obtained by the above time-consuming uneconomical measures were concentrations of calcium ascorbate dihydrate in nonhydrous hydroxypropane compounds too low to effect a marked increase in the effectiveness of calcium ascorbate when used medically, pharmaceutically and dermatologically, whereas, the process of the invention, in contrast thereto, produces not only similar but much higher concentrated and therefore more effective calcium ascorbate preparations by virtue of the formation of reaction products of calcium ascorbate dihydrate with nonhydrous hydroxypropane compounds and in such short time periods to amount only to a fraction of time heretofore consumed in obtaining mere solutions of calcium ascorbate dihydrate in the said nonhydrous hydroxypropane compounds as described above.

According to my invention as based upon the discovery that when nonhygroscopic calcium ascorbate dihydrate is reacted with a nonhydrous di- or trihydroxypropane e.g. 1,2-dihydroxypropane and trihydroxypropane at temperature exposure levels that will not cause the calcium ascorbate dihydrate to lose more than one molecule of its water of hydration, reaction products are formed that have far higher calcium ascorbate concentrations than would normally dissolve in the said nonhydrous hydroxypropane compounds, I prepared such reaction products which are also characterized by possessing new and extremely stable, clear and homogeneous and from fluid to solid consistencies with increasing calcium ascorbate concentrations to up to 82 parts by weight percent of the reaction products thus obtained during which the therein present nonhydrous hydroxypropene compound simultaneously provided the protective environment for the calcium ascorbate dihydrate during the said reaction therewith to render the same nondestructive at said reaction temperatures that will not cause the calcium ascorbate dihydrate to lose more than one of its molecules of water of hydration during the periods of time for such heating from 3 minutes to 10 minutes between a temperature range of from 225°Fa. and 255°Fa. depending on the increasing concentrations of calcium ascorbate dihydrate that must be reacted until no more crystals of the said calcium ascorbate dihydrate remain unreacted in the reaction mixture. The reaction starts as an endothermic reaction, requiring the input of heat to maintain the reaction temperature at reaction level during which the calcium ascorbate dihydrate slowly disappears under the constant agitation that must be applied. However, as soon as this has happened, an exothermic reaction sets in which must be strictly avoided and heating immediately discontinued and suitable cooling applied if the temperature rises beyond 255°Fa. in order to avoid the loss of the second molecule of water of hydration from the calcium ascorbate dihydrate which otherwise would automatically lead to the presence in the reaction product of an extremely unstable, medically and therapeutically most undesirable product. Such loss of the second molecule of water of hydration from the calcium ascorbate dihydrate can also be caused by unduly extending the period of reacting the reaction mixture, even at normal reaction temperatures between 225°Fa. and 255°Fa., after all of the calcium ascorbate dihydrate has been reacted. In forming the reaction product of the invention, only one molecule of water of hydration must be lost to the nonhydrous hydroxypropane compound by the endothermic reaction which first is observed. It is critical that the exothermic reaction following formation of the first reaction product be avoided. As the product of the reaction changes from the liquid and viscous to the solid state with increasing concentration of calcium ascorbate therein, the product remains the same, but its usefulness changes with its applicabilities in relation thereto. The total processing time for the reaction, including the possible preheating to reaction temperature and cooling below reaction temperature, ranges between no less than 30 minutes to no more than 75 minutes. There was still another property to the reaction products of the invention discovered, namely, at even the lowest calcium ascorbate concentrations they had lost all the irritant properties possessed originally by their constituent hydroxypropane compounds whichever was used therewith in forming the reaction products, so that even the most diluted solutions of the same containing relatively high proportions of irritant nonhydrous hydroxypropane compounds were free of irritant and harmful effects. The calcium ascorbate in the reaction product thus acted therein as a buffer particularly valuable for parenteral and anti-irritant, antiphlogistic, itch-relieving, anti-sensitizing, anti-dermatosic and other effects as described.

It is obvious thus that for the purposes of the invention only the nonhydrous form of hydroxypropane compounds can be suitable constituents of the novel calcium ascorbate dihydrate preparations as herein described. Furthermore, where the 1,2-dihydroxypropane is employed as the representative hydroxypropane compound constituent in such preparations instead of the trihydroxypropane, such preparations exhibit certain distinct advantages not possessed by preparations employing trihydroxypropane, in that they are practically nonsticky and endowed with antimicrobial properties. The employment of trihydroxypropane, however, has not less desirable properties than that of 1,2-dihydroxypropane though higher con-

centrated preparations exhibit a more or less desirable slight stickiness and then its antimicrobial properties amount to no more but some degree of a deterrent action, particularly against molds. Trihydroxypropane is nonfermentable. Used as constituent of parenteral preparations and as additive to drinks, trihydroxypropane is invaluable. Too, for use in stable cream or ointment preparations, the employment of trihydroxypropane, provided it is nonhydrous, it is preferable since in the making of such preparations containing therein the calcium ascorbate dihydrate preparations of the invention, it is absolutely essential that all ingredients in said creams or ointments, including the cream bases, are nonhydrous and free of water. Also noted is that no preparations of the invention requires the addition of any preservatives and, since they may be heated to sterilization temperatures without damage, as in the case of parenteral solutions of the invention, such solutions are, in effect, self-sterilizing, and may be diluted at will to any desired concentration of calcium ascorbate. Cream bases, employed in making creams and ointments containing calcium ascorbate preparations of the invention, must be soluble in and compatible with either of the hydroxypropane compounds employed in manufacturing said calcium ascorbate preparations of the invention used in forming said creams or ointments. Useful cream bases are edible fatty acid esters e.g. glyceryl - mono - laurate, glyceryl - mono - stearate, propylene - glycol-mono - laurate, propylene - glycol - mono-stearate and mannitan - mono - laurate which were tried with success, although creams and ointments prepared in such a manner are light sensitive and should be kept away from light wherein the fatty acid ester constituent base contains a small amount of emulsifying agent e.g. potassium hydroxide as is often the case in products of this nature. However, this light sensitivity is also an indication of the physiological activity and reactivity of the calcium ascorbate preparation used in making such creams and ointments, causing the release of active l-ascorbic acid or Vitamin C and ionic calcium in contact with living tissue by ionization. This is most desirable in utilizing the pharmacological properties of calcium ascorbate. It is not a sign of instability but of reactivity. The preparations of the invention can be stored for years without losing stability and reactivity potentials provided, of course, they are kept in receptacles that are nonreactive and noncatilytic, preferably in glass receptacles or glass-lined tanks for carrying out the reactions in manufacturing the reaction products of the invention representative of preparations of the invention. Metal containers should be avoided, as should be caps for glass or ceramic ware containers made of metal. Container caps should be preferably of Bakelite-like plastic materials (BAKELITE is a registered Trade Mark) for rigidity needed for caps, except, of course, other neutral plastics which must be nonpermeable to moisture and gas. The same may be said for neutral receptacles. Styrene resins may be used to advantage over polyethylene resins for rigidity and moisture nonabsorbability. Preperations of the invention have been kept in glass vials for many years, without the slightest changes in potencies or stabilities and despite frequent opening of the vials and reclosing the same and without hermetic exclusion of air folling reclosing.

The following examples of manufacturing the basic reaction product and preparations of the invention as well as of applicabilities for the same are presented for illustrative purposes only and not for limiting the scope of my invention.

Example of Method of Preparing the Reaction Product.

After weighing out the proper amounts of calcium ascorbate dihydrate and nonhydrous hydroxypropane compound constituents intended to be reacted with one another to form the reaction product of calcium ascorbate dihydrate with nonhydrous di- or trihydroxypropane compound e.g. 1,2-dihydroxypropane and trihydroxypropane, the weighed out constituents are mixed with one another and placed into a closable reaction vessel, preferably of glass or of glass-lined construction, and heated therein under constant agitation until the reaction is started and carried to completion. The reaction between calcium ascorbate dihydrate and the nonhydrous hydroxypropane compound in the reaction vessel starts when the temperature of about 225°Fa. is reached and is continued within the temperature range up to 255° Fa. which is the temperature exposure level for calcium ascorbate dihydrate at which the same will not lose more than one molecule of its water of hydration in the presence of the nonhydrous hydroxypropane compound providing simultaneously thereby a protective environment for said calcium ascorbate dihydrate constituent during the said reaction which is continued until all the crystals of calcium ascorbate dihydrate in the reaction mixture have disappeared thus indicating that the reaction is complete. This requires from 3 to 10 minutes time and depends largely on the temperature range and the concentration of calcium ascorbate dihydrate in the reaction mixture that must be reacted with the nonhydrous hydroxypropane compound therein. The resulting reaction product is a clear and homogeneous mass characterized by possessing, on cooling, extremely stable and from slightly viscous to solid consistencies depending, in degree, on the respective calcium ascorbate concentrations therein. Up to 82

parts by weight percent of the reaction product may be calcium ascorbate dihydrate in an active form and capable of releasing upon ionization in contact with living tissue active 1-ascorbic acid or Vitamin C and ionic calcium, and at least 18 parts by weight percent being the di- or tri-hydroxypropane compound. The time it takes to produce the reaction products of the invention is not less than 30 minutes and no more than 75 minutes, including preheating and cooling below the reaction temperature of the finished products, but depends also in this respect largely on the concentration of calcium ascorbate desired in the end product and increases with increasing such concentrations in such end products.

Some of the useful compositions of the reaction product of the invention made in the aforedescribed manner and useful as and in a variety of preparations, are the following, without thereby implying limitation thereto:

TABLE

Composition of reaction product by original ingredients	Examples of Compositions indicating parts by weight percentages					
	1	2	3	4	5	6
1,2-dihydroxypropane	92.5	90.0	85.0	80.0	—	—
trihydroxypropane	—	—	—	—	92.5	85.0
calcium ascorbate dihydrate	7.5	10.0	15.0	20.0	7.5	15.0
	7	8	9	10	11	12
1,2-dihydroxypropane	—	—	75.0	70.0	65.0	60.0
trihydroxypropane	80.0	75.0	—	—	—	—
calcium ascorbate dihydrate	20.0	25.0	25.0	30.0	35.0	40.0
	13	14	15	16	17	18
1,2-dihydroxypropane	—	—	—	—	28.0	26.0
trihydroxypropane	70.0	60.0	50.0	18.0		
calcium ascorbate dihydrate	30.0	40.0	50.0	82.0	72.0	74.0
	19					
1,2-dihydroxypropane	24.0					
calcium ascorbate dihydrate	76.0					

The compositions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 have increasing viscosities in that order and compositions 11 and 13 are very viscous and 12, 14 and 15 extremely viscous, whereas 16, 17, 18 and 19 are solids. Composition 16 is a tenacious solid product, but 17, 18 and 19 are brittle and easily pulverized to be added to other products, for instance candies or lozenges. All compositions are non-fermenting and the 1,2-dihydroxypropane preparations are also antimicrobial. Compositions with 1,2-dihydroxypropane are nonsticky but of acrid taste, whereas trihydroxypropane preparations are sweetish to slightly bitter in taste. A series of application compositions prepared with either compositions are presented in the following:

A) *A parenteral therapeutic calcium ascorbate solution*:

Solutions are prepared having in the reaction product originally but 7.5 parts by weight percent, on the total weight of the solution, of calcium ascorbate dihydrate with 92.5 parts by weight percent trihydroxypropane, as per the example 5 in the table. This slightly viscous solution is indefinitely stable and will supply per gram of solution 57 mgs active 1-ascorbic acid and about 7 mgs ionic calcium.

B) *A parenteral therapeutic calcium ascorbate solution*:

Solutions are prepared having in the reaction product originally but 25 parts by weight percent, on the total weight of the solution, of calcium ascorbate dihydrate with 75 parts by weight percent trihydroxypropane, as per the example 8 in the table. This viscous solution is indefinitely stable and may be diluted with distilled water for use if desired. It supplies 205 mgs of active 1-ascorbic acid and 23.7 mgs ionic calcium per gram of solution.

It is understood that any intermediate range in the calcium ascorbate content of these parenteral solutions may be substituted for either example. It overcomes the inherent instabilities of aqueous calcium ascorbate preparations which must contain preservatives and stabilizers which may be detrimental to health and increases the available concentration of calcium ascorbate for this purpose. Even if receptacles containing the parenteral solutions of the invention are frequently opened and closed, there is no danger of contamination as these new solutions are non-fermentable. However, receptacles should be glass and it is advisable to keep light out during storage. Too, the receptacles should have plastic caps to avoid contact with metals which may catalyze ionization reactions of the calcium ascorbate constituent of the reaction product of the parenteral solutions of the invention.

Injected calcium ascorbate is readily utilized in metabolism and provides a reservoir of Vitamin C in the adrenal glands. It is indicated for intensive treatment of Vitamin C deficiencies including early and subclinical scurvy, also indicated in calcium deficiencies.

C) *Liniment-type calcium ascorbate*:

Solutions are prepared having in the reaction product originally from 7.5 parts to 40 parts by weight percent, on the total weight of the solution, of calcium ascorbate dihydrate with from 92.5 parts by weight to 60 parts by weight of 1,2-dihydroxypropane, as per examples 1, 2, 3, 4, 9, 10 in the table. These slightly viscous to viscous solutions are extremely stable and supply from 57 mgs to 328 mgs active 1-ascorbic acid and from 7 to 38 mgs ionic calcium per gram of solution.

It is understood that any further intermediate range in calcium ascorbate content of these solutions may be substituted without thereby limiting the scope of the invention. These solutions are valuable agents for application to sores, wounds, burns, bruises, cuts and cracks of the skin and lips, to itching skin conditions and dermatosic and infected areas of the skin including such due to hypocalcemia. They are hemostatic, antiphlogistic, antitraumatic, antisensitizing, antidermatosic, soothing and itch-relieving as well as antimicrobial. For each purpose separate products may be supplied to the trade, for instance as lip-anticracking agent, as hemostatic agent, as anti-traumatic agent, as anti-irritant agent, as anti-itch agent or anti-burn agent. These preparations have all the properties of calcium ascorbate and its ionization products 1-ascorbic acid and ionic calcium as well as the antimicrobial properties of 1,2-dihydroxypropane. The high concentrations of available calcium ascorbate in the stable form allows attainment of increased therapeutic effects from calcium ascorbate where applied as medical, therapeutic or antidematosic agent and not attainable with aqueous preparations. It is understood that instead of the 1,2-dihydroxypropane also the trihydroxypropane may be used, except that such preparations are more or less sticky and possess no antimicrobial properties, whereas preparations with 1,2-dihydroxypropane are non-sticky and possess antimicrobial properties. Too, all the preparations, made with either the 1,2-dihydroxypropane or trihydroxypropane as constituent of the reaction product of the invention, are non-irritant to the skin, in contrast to the irritant effects the nonhydrous hydroxypropane derivatives themselves exert when in contact with the skin. This includes preparations with even less than 7.5 parts by weight percent, on the total weight of the preparation, of calcium ascorbate. Thus, a lip-anticracking agent may have 7.5 to 10 parts by weight percent calcium ascorbate; a hemostatic agent may have 20 to 40 parts by weight calcium ascorbate; an anti-traumatic agent may have 15 to 20 parts by weight calcium ascorbate and be used as packing application to bruises, e.g. soaked in cotton fabric; an anti-irritant agent may be supplied as a 5 to 10 parts by weight calcium ascorbate containing preparation and rubbed into the skin or laid upon the skin and permitted to be slowly absorbed; an anti-itch agent may contain from 4 to 10 parts by weight calcium ascorbate and applied directly to the itching skin sections, bringing almost immediate relief; an anti-burn agent may contain from 10 to 30 parts by weight calcium ascorbate but primarily as the reaction product with trihydroxypropane unless, too, the presence of an antimicrobial agent is desired, which requires the use of the 1,2-dihydroxypropane in the reaction product. Preparations to be applied to sores and wounds generally include concentrations with from 7.5 to 10 parts by weight calcium ascorbate and preparations useful against cuts are the same as against bleeding, using the hemostatic agent with from 20 to 40 parts by weight calcium ascorbate. In hypocalcemic conditions and cermatosic conditions caused by such, high calcium concentrations are required in the preparations to be effective and from 20 parts by weight to 40 parts by weight of calcium

ascorbate therein should be the rule in order to obtain, upon constant application to such conditions for a relatively long period of time, success, which is co-incident with an increase in the metabolic and blood calcium rate.

D) *Anti-cariogenic calcium ascorbate drink additive*:

Solutions are prepared having from 7.5 parts to 20 parts by weight calcium ascorbate in the reaction product with from 92.5 to 80 parts by weight of trihydroxypropane, as per examples 5, 6 and 7 in the table and supplying from 57 mgs to 164 mgs active 1-ascorbic acid and from 7 to 19 mgs ionic calcium.

These solutions are to be added to drinks which have cariogenic properties e.g. sodas, lemonades and fruit juices. In doing so, they will counteract these cariogenic properties and thus help to protect the drinker from suffering cariogenic effects. At the same time, however, the drink is enriched by active Vitamin C and calcium additions and so is not only healthier but also preventing caries formation or retarding caries formation. Additions may also be made to milk in the lukewarm or cold condition to enrich the same with Vitamin C and calcium, without curdling up. Curdling will start, however, as soon as the milk is heated, indicating the ready availability of the ionization products 1-ascorbic acid and calcium to the system, as the same ionization takes place also in the body. A few drops of this additive will suffice to fill the daily requirement for Vitamin C. Using of additives having less than 7.5 parts by weight percent calcium ascorbate in the reaction product will not be a deviation from the scope of this invention, except that it would make its use more economical and saleable. Aqueous calcium ascorbate additions would not be useful because of the instable character of the same, it could not be stored for any length of time and decomposition products would form on repeated opening and closing of any receptables marketed containing such aqueous solutions. Contrary to this, the products of the invention are stable and not subject to deterioration on repeated opening and closing and can be kept for long period of time on the shelf.

E. *Therapeutic calcium ascorbate skin cream*:

Solutions of slight to very viscous consistencies of the reaction product and containing from 7.5 parts by weight to 50 parts by weight calcium ascorbate with from 92.5 to 50 parts by weight trihydroxypropane, as per examples 5, 6, 7, 8, 13, 14, 15 in the table, are combined through thorough mixing and homogenizing with a nonhydrous cream-base material which is an edible fatty acid ester e.g. glyceryl-mono-laurate, propylene-glycol - mono - laurate, glyceryl - mono-stearate, propylene - glycol - mono - stearate and mannitan - mono - laurate, whereby it is essential that these cream-base materials are soluble in and compatible with the trihydroxy-propane or 1,2-dihydroxypropane which may be used in place of the trihydroxypropane when antimicrobial properties are desired in the creams prepared therewith.

To form creams, the cream-base material must be used in an amount of from 12.5 parts by weight to 40 parts by weight, on the total weight of the cream, with from 87.5 parts by weight to 60 parts by weight of the reaction product making up the remainder. This enables the formation of a wide variety of creams with a wide variety of calcium ascorbate contents, in fact, it enables the first formation of smooth and elegant creams containing calcium ascorbate capable of ionizing in contact with living tissue to supply from 34 mgs to 350 mgs active 1-ascorbic acid or Vitamin C and from 4 mgs to 40 mgs ionic calcium per gram of cream.

Absolutely stable skin creams may be prepared but must be protected from light and the ingredients must be free from catalytically active metals. Too, they must be packed in light protective material, free from metal ingredients and the caps must not be metal caps. For ointment use as may be desirable by a physician, shorter-life creams may be made by using other than the preferred cream-base materials, without affecting the effectiveness of calcium ascorbate as a pharmaceutical agent but failing to possess so-called cosmetic elegance. Generally, no white creams can be produced with calcium ascorbate but they have cosmetic elegance and serve the purpose as antidermatosic and therapeutic agents. The creams are useful for the same purposes and applications as the liniment-type calcium ascorbate solutions are, except, in a cream form, they are stiffer and more substantive even in low calcium ascorbate concentrations. Creams don't run, solutions run.

Some of the creams' compositions are as follows:

TABLE OF CREAM COMPOSITIONS

Ingredients	A	B	C	D	E	F	G	H
Glycerylmonolaurate	40.0	—	—	—	—	40.0	20.0	—
Glycerylmonostearate	—	15.0	—	—	—	—	—	—
Propyleneglycolmonostearate	—	—	15.0	—	—	—	—	—
Propyleneglycolmonolaurate	—	—	—	12.5	—	—	—	30.0
Mannitanmonolaurate	—	—	—	—	12.5	—	—	—
Reaction Product No. 5 7.5%	—	—	—	—	—	60.0	—	—
Reaction Prod. No. 7 20%	—	85.0	85.0	—	—	—	80.0	—
Reaction Prod. No. 12 30%	60.0	—	—	—	—	—	—	—
Reaction Prod. No. 14 40%	—	—	—	—	87.5	—	—	—
Reaction Prod. No. 15 50%	—	—	—	87.5	—	—	—	70.0

These examples shall not be considered restrictive to the scope of the invention and a great many variations are possible, including additions of perfumes, and other ingredients that are inert to the calcium ascorbate constituent in the reaction product employed in preparing same. Too, the employed reaction products may be replaced by any of those containing 1,2-dihydroxypropane, for instance No. 1 for a 7.5%, No. 4 for a 20%, No. 10 for a 30% and No. 12 for a 40% calcium ascorbate containing reaction product as listed in the table referring to examples of reaction products.

In preparing the creams, I first weigh out the ingredients and add the reaction product to the molten cream base at about a temperature range between 100°Fa. and 150°Fa. and mix properly and homogenize. The creams are then filled into neutral receptacles, that is receptacles which are of an inert material with respect to calcium ascorbate, that is porcelain or glass, or non-porous plastics, with plastic covers. Too, the material must be proof against light penetration and be stored in the dark if possible. The resulting creams are smooth and elegant and serve their purposes as for use in the treatment of sores, wounds, burns, bruises, cuts and cracks of the skin and lips, itching and dermatosic skin conditions including such due to hypocalcemia, particularly exerting the therapeutic properties of calcium ascorbate and its ionization products formed in contact with living tissue i.e. ionic calcium and 1-ascorbic acid or Vitamin C. The hemostatic, antiphlogistic, antitraumatic, antisensitizing and antidermatosic, soothing and itch alleviating effects of the new creams are outstanding and the creams are also antimicrobially effective where instead of trihydroxypropane the 1,2-dihydroxypropane is the constituent in the reaction product employed in preparing the creams.

F) *Suckable therapeutic calcium ascorbate*:

Reaction products are prepared from 72 parts to 78 parts by weight, on the total weight of the reaction product, of calcium ascorbate dihydrate with the nonhydrous 1,2-dihydroxypropane making up the remainder, as per examples 17, 18 and 19 in the table. They are solid, homogeneous, clear and hard candy-like in consistency and very brittle. They supply per gram reaction product from 590 gms to 639 gms of active 1-ascorbic acid and from 68.4 to 74.1 mgs ionic calcium upon ionization of its containing calcium ascorbate constituents therein. These hard and solid materials are shaped or cast in the process of reaction after the reaction is complete directly into final configurations such as candies to be sucked in the mouth by application of pressure and cooling. The suckable products thus obtained have a strong mucolytic effect in the mouth and throat cavities, they act antimicrobial by virtue of high local concentration of applied 1-ascorbic acid which is known to act antiviral and antibactorial by itself. In addition, liberated 1,2-hydroxypropane on sucking, too, enhances this effect by its own antimicrobial potency. It is extremely effective in sore throats and gives immediate relief. It is noncariogenic.

G) *Noncariogenic lozenges with calcium ascorbate*:

T sugar and other essential candies or lozenges ingredients are added and properly

and thoroughly mixed from 0.5 to 20 parts by weight, on the total weight of the candies or lozenges mass, of either reaction product having from 72 to 78 parts by weight percent, on the total weight of the reaction product, calcium ascorbate dihydrate and from 28 to 22 parts by weight of 1,2-dihydroxypropane. The candies or lozenges are formed, after mixing in the desired amounts of the reaction product, in the usual manner, packed and shipped. The added reaction product supplies from about 3 mgs to 127 mgs active 1-ascorbic acid or Vitamin C and from 0.34 to 14.8 mgs ionic calcium upon ionization of its constituent calcium ascorbate therein. Ionization takes place in the mouth in contact with living tissue and tissue fluids. The effect of sugar and other constituents in the candies and lozenges that may be procariogenic are being counteracted by the presence of the anticariogenic calcium ascorbate in form of its reaction product therein. This reaction product is made to a fine powder before mixing with the other ingredients and enhances the antimicrobial, antiphlogistic, anti-inflammatory and other desirable properties of lozenges and candies by adding its own proven properties, respectively those of calcium ascorbate, particularly with respect to its antipyorrheic effectiveness upon inflammatory oral conditions in the mouth and gums.

WHAT I CLAIM IS:—

1. A method of preparing the reaction product of calcium ascorbate dihydrate with a monohydrous di- or trihydroxypropane compound which comprises reacting the admixed calcium ascorbate dihydrate and nonhydrous hydroxypropane compound in a closed vessel, under agitation, at a reaction temperature of from 225 to 255°F in the presence of a protective, non-destructive environment for the necessary period of time for formation of a clear, homogeneous and stable reaction product of calcium ascorbate.

2. A method as claimed in claim 1 substantially as described herein.

3. A method as claimed in claim 1 substantially as described herein with reference to the Examples.

4. The reaction product obtained by a method as claimed in any of claims 1—3.

5. A preparation comprising a reaction product as claimed in claim 4 of up to 82 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

and at least 18 parts by weight percent, on the total weight of the reaction product, of a nonhydrous di- or tri- hydroxypropane compound each gram of the said preparation supplying up to 672 mg of active 1-ascorbic acid and up to 78 mg of ionic calcium.

6. A preparation as claimed in claim 5 in which the hydroxypropane is 1,2-dihydroxypropane.

7. A preparation as claimed in claim 5 in which the hydroxypropane is trihydroxypropane.

8. A parenteral therapeutic agent containing a preparation as claimed in claim 7 comprising the reaction product of from 7.5 to 25 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 92.5 to 75 parts by weight percent of nonhydrous trihydroxypropane each gram of the said agent supplying from 57 to 205 mg active 1-ascorbic acid and from 7 to 23.7 mg ionic calcium.

9. A liniment-type nonhydrous therapeutic agent containing a preparation as claimed in claim 6 comprising the reaction product of from 7.5 to 40 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 92.5 to 60 parts by weight percent of nonhydrous 1,2-dihydroxypropane each gram of the said agent supplying from 57 to 328 mg active 1-ascorbic acid and from 7 to 38 mg ionic calcium.

10. An anticariogenic additive for drinks containing a preparation as claimed in claim 7 comprising the reaction product of from 7.5 to 20 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 92.5 to 80 parts by weight percent of nonhydrous trihydroxypropane each gram of the said additive supplying from 57 to 164 mg active 1-ascorbic acid and from 7 to 19 mg ionic calcium.

11. A suckable therapeutic agent containing a preparation as claimed in claim 6 comprising the reaction product of from 72—78 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 28 to 22 parts by weight percent of nonhydrous 1,2-dihydroxypropane each gram of the said agent supplying from 590 to 639 mg active 1-ascorbic acid and from 68.4 to 74.1 mg ionic calcium.

12. A nonhydrous therapeutic skin cream containing from 60 to 87.5 parts by weight percent, on the total weight of the cream, of

a preparation as claimed in claim 7 thoroughly compounded with from 40 to 12.5 parts by weight percent, on the total weight of the cream, f glyceryl - mono - laurate, glyceryl-mono - stearate, propylene - glycol - mono-laurate, propylene-glycol-mono-stearate or mannitan - mono - laurate, the said preparation comprising the reaction product of from 7.5 to 50 parts by weight, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 92.5 to 50 parts by weight percent, on the total weight of the reaction product, of nonhydrous trihydroxypropane each gram of the said cream supplying from 34 to 350 mg active 1-ascorbic acid and from 4 to 40 mg ionic calcium.

13. A noncariogenic candy or lozenge containing normal sugar and other essential candy and lozenge ingredients, containing from 0.5 to 20 parts by weight percent, on the total candy weight, of a preparation as claimed in claim 6 thoroughly intermixed with from 99.5 t 80 parts by weight percent, on the total candy weight, of normal sugar and other essential candy and lozenge ingredients, the said preparation comprising the reaction product of from 72 to 78 parts by weight percent, on the total weight of the reaction product, of calcium ascorbate dihydrate of the formula

$$(C_6H_7O_6)_2.Ca.2H_2O$$

with from 28 to 22 parts by weight percent, on the total weight of the reaction product, of nonhydrous 1,2-dihydroxypropane each gram of the said candy supplying from 3 to 127 mg active 1-ascorbic acid and from 0.34 to 14.8 mg ionic calcium.

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